Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for perindopril, the scientific conclusions are as follows:

Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH)
In view of available data on SIADH from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between perindopril and SIADH is at least a reasonable possibility. The PRAC concluded that the product information of products containing perindopril should be amended accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction 'Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH)' with a frequency 'rare'. The Package leaflet is updated accordingly.

Depression
In view of available data on depression from clinical trials, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, PRAC considers a causal relationship between perindopril and depression established. The PRAC concluded that the product information of products containing perindopril should be amended accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction 'depression' with a frequency 'uncommon'. The Package leaflet is updated accordingly.

Flushing
In view of available data on flushing from clinical trials, the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between perindopril and flushing established. The PRAC concluded that the product information of products containing perindopril should be amended accordingly.

Update of section 4.8 of the SmPC to add the adverse reaction 'flushing' with a frequency 'rare'. The Package leaflet is updated accordingly.

Anuria/oliguria
In view of available data on anuria and oliguria from spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between perindopril and anuria and oliguria established. The PRAC concluded that the product information of products containing perindopril should be amended accordingly.

Update of section 4.8 of the SmPC to add the adverse reactions 'anuria' and 'oliguria' with a frequency 'rare'. The Package leaflet is updated accordingly.

Acute renal failure
In view of available data on acute renal failure from clinical trials, the PRAC considers a causal relationship between perindopril and acute renal failure established. The PRAC concluded that the product information of products containing perindopril should be amended accordingly.

Update of section 4.8 of the SmPC to amend the adverse reaction 'acute renal failure' from frequency 'very rare' to frequency 'rare'. The Package leaflet is updated accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for perindopril the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing perindopril is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing perindopril are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.8

The following adverse reaction should be added under the SOC 'Endocrine disorders' with a frequency 'rare':

Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

~~Cases of syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported with other ACE inhibitors. SIADH can be considered as a very rare but possible complication associated with ACE inhibitor therapy including perindopril.~~

The following adverse reaction should be added under the SOC 'Psychiatric disorders' with a frequency 'uncommon':
Depression

The following adverse reactions should be added under the SOC 'Renal and urinary disorders' with a frequency 'rare':
Anuria/Oliguria

The following adverse reaction should be added under the SOC 'Vascular disorders' with a frequency 'rare':
Flushing

The frequency of the adverse reaction 'acute renal failure' should be changed to 'rare'

Package Leaflet

- Section 4

Tell your doctor if you notice any of the following side effects:

Uncommon
Depression

Rare
Dark urine, feeling sick (nausea) or being sick (vomiting), muscle cramps, confusion and seizures. These may be symptoms of a condition called SIADH (inappropriate antidiuretic hormone secretion).

Decreased or absent urine output

Flushing

Acute renal failure [changed from frequency 'very rare']

~~Concentrated urine (dark in colour), feel or are sick, have muscle cramps, confusion and fits which may be due to inappropriate ADH (anti-diuretic hormone) secretion can occur with ACE inhibitors.~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	8 August 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	7 October 2021